Current HIV/AIDS Reports (2019) 16:423–430
https://doi.org/10.1007/s11904-019-00468-z

THE GLOBAL EPIDEMIC (SH VERMUND, SECTION EDITOR)

Evolving HIV Epidemiology in Mainland China: 2009–2018

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Published online: 26 November 2019

Abstract

Purpose of Review This review is intended to provide an overview of the evolution of HIV epidemiology over the past decade in China.

Recent Findings We provided a succinct overall view of the epidemic, followed by surveillance data, profiles of key populations, HIV molecular epidemiology, and drug resistance, as well as survival in the age of antiretroviral therapy usage. For each topical issue, we first reviewed the latest empirical evidence, followed by a brief summary assessment. We briefly addressed the challenges and opportunities of the next generation of HIV control and prevention efforts in China.

Summary Notably, macro-social factors need to be integrated into the next generation of clinical and/or behavioral HIV research to inform disease progression and management, as well as control and prevention.

Keywords Epidemiology · HIV · China

Introduction

In 2011, the State Council of the People's Republic of China implemented "Five Expansions and Six Strengthens," for HIV/AIDS prevention and control [1]. In brief, this report recommends nationwide expansions to strengthen coverage in 11 areas: (1) health education; (2) testing and surveillance; (3) prevention of mother-to-child transmission; (4) comprehensive interventions; (5) antiretroviral therapy (ART); (6) blood administration and safety; (7) medical security; (8) health care and social support; (9) protection of rights and interests for HIV/AIDS patients and their families; (10) organizational leadership; and (11) strengthening of response team for HIV control. This report has guided the implementation of two consecutive 5-year action plans to control HIV/AIDS (2011–2015; 2016–2020).

With the lifespan of people living with HIV (PLWH) approximating those of the general population, amidst the changing profile of risk-taking subgroups, the emergence of new HIV subtypes and the urgency of initiating antiretroviral therapy (ART) upon an HIV diagnosis are likely to have significant impact on the HIV epidemic in China. With this backdrop, this review is intended to provide an overview of the evolution of HIV epidemiology over the past decade in China.

For this review we combed both the Chinese- and English-language scientific literature using the broad term "HIV epidemiology in China." This search has resulted in 6 broad topical issues. In brief, we first provided a succinct overall review of the epidemic, followed by surveillance data, profiles of key populations, HIV molecular epidemiology, and drug resistance as well as survival in the age of ART usage. For each topical issue, we first reviewed the latest empirical evidence, followed by a brief summary assessment. We

This article is part of the Topical Collection on *The Global Epidemic*

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then briefly addressed the challenges and opportunities of the next generation HIV control and prevention efforts in China.

Annually Reported HIV Epidemic

Number of Newly Identified HIV-Positive Cases

According to China's Center for Disease Control and Prevention (CDC), 276,335 HIV-positive cases had been reported by the end of 2008, of whom 38,150 were dead. Among the 238,185 PLWH at the end of 2008, 47,134 (19.8%) were receiving ART. In 2009, a total of 68,249 HIV-positive cases were newly identified. Since then, the annually reported number of newly identified HIV-positive cases has been steadily increasing year by year and reached 148,589 in 2018 [2]. Between 2009 and 2018, the number of persons testing for HIV increased from 55.6 to > 240 million [2]. At the end of 2018, there were 861,042 PLWH in China [2].

In brief, the upward trend in the annual number of newly identified HIV-positive cases is most likely attributable to increasing efforts addressing HIV screening and testing.

HIV Transmission Patterns

In 2009, HIV infection attributable to sexual activities had become the dominant mode of transmission (57.4%), followed by injection drug use (IDU) at 25.2%. The proportion of heterosexual and homosexual transmission increased from 48.3% and 9.1% in 2009 to 71.5% and 23.3% in 2018. The proportion of HIV transmission by IDU declined substantially from 25.2% in 2009 to 3% in 2018 [2].

The shift from IDU and blood transfusion to sexual transmission as the dominant mode of HIV infection now requires different control and prevention strategies.

Geographical Distribution

There is a substantial regional variation across China in the number of HIV infections. The earliest HIV epidemic in China started with an outbreak reported in 1989 among 146 infected heroin users in Yunnan province, near China's southwest border [3, 4], and then spread along the drug trafficking route from western to central and eastern areas. Among the 32 provinces in Mainland China, 5 provinces including Sichuan, Yunnan, Guangxi, Guangdong, and Henan ranked as the highest in terms of the identifiable number of PLWH at the end of 2018 [2, 5]. Except for Henan province from central China where the majority of PLWH are commercial plasma donors and infected through blood transfusion in the early 1990s [6], the other 4 provinces are all from western and southern China.

The initial epidemic was localized in provinces (especially in southwest regions) with high rates of drug use. Now the epidemic has spread to the rest of the country.

HIV Testing and Surveillance

Since 2004, the government of China has launched a multi-pronged national program to actively identify key populations thought to be at high risk for HIV infection [7] to engage in (a) voluntary counseling and testing [8]; (b) opt-out testing for clinical patients [9]; (c) provider-initiated testing and counseling [10]; and (d) home-based and community-based testing [11]. The overall person-times of HIV testing increased over four-fold from 55.6 million in 2009 to > 240 million in 2018, whereas HIV positivity decreased from 0.11% in 2009 to 0.06% in 2018.

In 2010, the National Center for AIDS & STD Control and Prevention of China's CDC revamped the national HIV sentinel surveillance system by establishing around 1,880 surveillance sites targeting six key populations: (1) men who have sex with men (MSM); (2) drug users (DUs); (3) female sex workers (FSWs); (4) male attendants of sexually transmitted disease (STD) clinics; (5) pregnant women; and (6) long-haul truck drivers. In each site, approximately 400 persons were tested for HIV. Between 2009 and 2018, the HIV-positive rate via sentinel surveillances was relatively constant at around 1.0% overall, ranging from 5.4 to 6.95% among MSM; 6.24 to 2.66% for DUs; 0.6 to 0.2% for FSWs; 0.5 to 0.8% for male STD clinic attendants; 0.2 to 0.1% for pregnant women; and 0.03 to 0.07% for long-haul truck drivers [2].

Knowing one's HIV status is the first step to accessing care and preventing further infection [12]. The testing initiative has resulted in more testing uptakes.

HIV Risks Among Key Populations

Men Who Have Sex with Men

In a cross-sectional survey conducted between February 2008 and September 2009 in 61 cities in China, the overall HIV prevalence was 4.9% (95% CI, 4.7–5.1%) among a total of 47,231 MSM [13]. A number of cross-sectional surveys have been conducted in various areas across the country, in which the rate of HIV prevalence among MSM ranges from 2.6 to over 10%, depending on the study area and sample size [14–28].

The HIV incidence among MSM is also high compared with other populations. Feng et al. [29] performed a meta-analysis of 24 studies published between 2010 and 2015, yielding a pooled incidence of HIV infection of 5.0/100

person year (PY). Severe epidemic areas have higher HIV incidence than other areas (4.9/100 PY vs. 3.4/100 PY).

Recent studies using serial cross-sectional surveys or cohort study design or estimation based on BED HIV-1 capture enzyme immunoassay (BED-CEIA) indicate that the HIV incidence among MSM varies from 3.5 to > 10.0/100 PY [14, 16, 30–33]. Low education level, minority ethnic group, unprotected anal sex, commercial sex, multiple sexual partners, recreational drug use, anal bleeding, syphilis infection, and history of herpes simplex virus type 2 (HSV-2) infection are associated with HIV incidence or recent infection among MSM [14, 16, 29–33].

MSM are the highest-risk group for HIV infection in China. Improving HIV surveillance and expanding HIV interventions for Chinese MSM individuals are essential [34].

Female Sex Workers

A systematic review and meta-analysis reveal that the national HIV prevalence among FSWs has declined from 0.74% (95% CI, 0.37–1.49%) between 2000 and 2002 to 0.40% (95% CI, 0.31–0.53%) between 2009 and 2011; however, southwest China still bore the greatest HIV disease burden in this population [35].

Recent sentinel surveillances reveal that the overall prevalence of HIV infection among FSWs has declined to around 0.2% in the past 5 years [2]. However, HIV prevalence among FSWs varies drastically by regions. For example, Zhu et al. [36] reported that very high prevalence of HIV infection was observed among both FSWs (2.74%) and their male clients (2.62%) in the China-Vietnam border region of Yunnan province in southwest China, where herpes simplex virus type 2 (HSV-2) infection was a risk factor for HIV infection in FSWs and male clients.

Due to low retention rate, HIV incidence of FSWs has rarely been directly observed. Instead, using BED-CEIA, the HIV incidence among FSWs in Sichuan province in west China was estimated to be 0.22% (95% CI, 0.16–0.28%) during 2011 to 2015 [37]. In Dehong Prefecture, a China-Myanmar border region in Yunnan province, the HIV incidence among FSWs from 2009 to 2017 was estimated based on 18,126 FSWs recruited by fingerprint technique. That is, between 2009 and 2011, 2012 and 2014, and 2015 and 2017, estimated HIV incidence was 0.22% (95% CI, 0–0.64%), 1.24%(95% CI, 0.15–2.32%), 0.55% (95% CI, 0.01–1.08%) among Myanmar FSWs, respectively; 0.62% (95% CI, 0.25–0.98%), 0.11% (95% CI, − 0.04–0.26%), 0.22% (95% CI, 0–0.44%) among Chinese FSW, respectively [38].

Although FSWs have moderate to low HIV prevalence, higher prevalence is observed in localized epidemics such as the China-Vietnam border. An accurate depiction of the epidemic in this population is obscured due to the lack of data on incidence.

Older Males

Between 2010 and 2018, the annual number of newly reported HIV-positive males aged 60 years or older increased by > 5-fold from 4751 to 24,465, and the proportion of newly reported HIV-positive cases who were 60 years or older males increased from 7.41% in 2010 to 16.46% in 2018 [2]. The majority of them were infected through heterosexual contacts, very likely owing to low knowledge of HIV/AIDS and low awareness of HIV risks among the general older population in China [39].

Chen et al. [40] conducted a large-scale, population-based cohort study in rural southwest China where 722,795 adults > 20 years old participated in the baseline survey between 2012 and 2013 and 493,990 (69%) of them completed the one-year follow-up survey between 2014 and 2015. While the overall HIV incidence was 2.73 (95% CI, 2.38–3.08) per 10,000 PY (235/860,627 PY), the HIV incidence was 71.28 (95% CI, 35.21–107.35) per 10,000 PY among males aged 50 to 69 years who had less than secondary schooling and were divorced or widowed.

Using an administrative data source (2008 to 2014) from the Shanghai Municipal CDC, Ning et al. found that HIV prevalence ranged between 4.9% and 15.4% among men aged 50 and above [26]. Moreover, in 2014, MSM participants had a higher HIV prevalence than non-MSM (4.9% vs 1.8%), whereas syphilis was higher in older non-MSM compared with MSM (18.7% vs 12.4%).

There is emerging evidence that older men have been increasingly and disproportionally affected by HIV in the past decade in this country [41, 42].

College Students

An increase of HIV infection among college students (mostly males) was observed with an annual growth rate ranging from 30 to 50% during late 2000s through early 2010s [43•]. Fortunately, such an upward trend seems to be contained since 2015, which could be very likely attributed to proactive and tailored HIV prevention and intervention efforts [43].

Spouses of HIV-Positive Patients

A long-term intervention trial among a large sample of serodiscordant couples in Yunnan province [44, 45] has demonstrated that ART usage among the HIV-positive spouses could substantially reduce secondary HIV transmission within the serodiscordant couples. According to China's CDC [2], the coverage of ART for serodiscordant couples has increased from 58.1% in 2011 to 92.2% in 2018, and correspondingly, the HIV seroconversion rate among HIV-negative spouses has decreased from 2.60% in 2011 to 0.55% in 2018 while

excluding the Lianshan Prefecture of Sichuan province from analysis.

Adherence to ART by the HIV-positive spouses can significantly reduce the odds of infection among HIV-negative spouses.

Molecular Epidemiology

HIV-1 Subtypes

The third nationwide molecular epidemiological survey conducted among 1408 HIV-positive persons newly diagnosed in 2006 across the country indicated that over 11 genetic variants were circulating which were associated with different geographical regions and modes of transmission, and CRF01_AE, CRF07_BC, CRF08_BC, and subtype B accounted for 92.8% of HIV-1 variants [46].

Yuan et al. [47] conducted a systematic review and meta-analysis to provide a comprehensive prevalence estimate of different HIV-1 subtypes in sexual transmission by 2016 in China. A total of 130 eligible studies were identified, including 18,752 successfully genotyped samples. The pooled prevalence of CRF01_AE, subtype B, CRF07_BC, CRF08_BC, and subtype C were 44.54% (95% CI, 40.81–48.30%), 18.31% (95% CI, 14.71–22.17%), 16.45% (95% CI, 13.82–19.25%), 2.55% (95% CI, 1.56–3.73%), and 0.37% (95% CI, 0.11–0.72%), respectively. The prevalence of subtype B in sexual transmission decreased, while the prevalence of CRF01_AE and CRF07_BC in sexual transmission and CRF08_BC in heterosexual transmission increased. HIV-1 subtype distribution varied significantly between regions.

To elucidate the geographic and dynamic change of HIV-1 subtypes through heterosexual transmission, Xiao et al. [48] did a systematic review and meta-analysis of 42 heterosexual transmission studies identified by searching electronic databases through August 2016, and the study period range was from 1992 to 2014. The overall prevalence of CRF01_AE, CRF07_BC, B/B′, CRF08_BC and C during 1992 to 2014 was 46.34%, 19.16%, 13.25%, 10.61%, and 4.29%, respectively. The prevalence of CRF01_AE and CRF07_BC increased, and the prevalence of CRF07_BC and CRF08_BC have exceeded that of B/B′ since 2010. A significantly higher prevalence of CRF01_AE was found in the southern provinces, CRF07_BC in eastern provinces, CRF08_BC and C in southwest provinces, and B/B′ in northern provinces [48].

Recently, in a meta-analytic integration of 66 molecular epidemiological studies published between January 2007 and December 2017, Yin et al. [49] found temporal and geographical trends in the HIV-1 epidemic among Chinese MSM. CRF01_AE (57.36%, 95% CI, 53.76–60.92%) was confirmed as the most prevalent HIV-1 subtype among MSM in China, steadily increasing prior to 2012 but decreasing during 2012–2016. CRF07_BC increased over time whereas B/B′ decreased over time. CRF55_01B has increased in recent years, with higher pooled estimated rate in two southern provinces: Guangdong (12.22%) and Fujian (8.65%).

The distribution of HIV-1 subtypes is highly diverse and complex in China. The complex and diverse HIV-1 subtypes prevalent in both heterosexual and homosexual transmissions underscore urgent need for molecular monitoring of HIV transmission and intensified HIV prevention and control in China.

HIV Drug Resistance

Liu et al. [50] conducted a systematic review and meta-analysis of emergent HIV drug resistance (HIVDR) among a total of 2908 participants from 12 cohort studies and 6553 participants from 13 cross-sectional studies through February 2014. The pooled prevalence of HIVDR from longitudinal cohort studies was 10.79% after 12 months of combination antiretroviral therapy (cART) and 80.58% after 72 months of cART. The pooled prevalence of HIVDR from cross-sectional studies was 11.1% during the 0–12 months ART treatment interval, and increased to 22.92% at 61–72 months. Higher HIVDR prevalence was observed among patients infected through former plasma donation or IDU than those infected through sexual transmission. Other studies [51, 52] reveal that acquired HIVDR is highly prevalent among patients with ART failure.

There is a growing concern regarding transmitted drug resistance (TDR) or pretreatment drug resistance (PDR) among treatment-naive patients in China. A nationwide cross-sectional survey was conducted among 5627 ART naive, newly diagnosed HIV-infected individuals in 2015 in China, where TDR mutations were found in 3.6% of the cases, with 1.1% harboring TDR to protease inhibitors (PIs), 1.3% having TDR to nucleoside reverse transcriptase inhibitors (NRTIs), and 1.6% to non-nucleoside reverse transcriptase inhibitors (NNRTIs) [53].

The prevalence of TDR has been extensively investigated in various regions in the past 5 years which reveals a complex pattern throughout the country. For example, the prevalence of TDR was reported to be 6.0% (18/302) in Henan province during 2013–2014 [54]; 7.8% (16/205) in Tianjin during 2014–2017 [55]; 11.1% (17/153) in Zhejiang province during 2014–2017 [56]; 6.12% (57/932) in Beijing during 2014–2015 [57]; 6.1% (33/542) in Hebei province during 2014–2015 [58]; 5.5% (10/183) in Guangxi in 2015 [59]; 17.4% (55/317) in Shanghai in 2017 [60•]; and 9.9% (46/464) in Sichuan province during 2017–2018 [61].

The rapid scaling up of cART is the concern about HIVDR. High prevalence of HIVDR would restrict therapy options, compromise the effect of current therapy regimens, and increase the risk of treatment failure. This is particularly problematic in China where access to protease inhibitors (PIs) and new classes of antiretroviral drugs (ARV) is still limited. TDR mutations are mainly due to NNRTIs and NRTIs, due to limited access to protease inhibitors (PIs) in China.

Antiretroviral Therapy and Survival

China's National Free Antiretroviral Treatment Program (NFATP) began in 2002. Presently, the 4th edition of the *China's national guidelines for NFATP* serves as the standard national reference, with continuous updates in regimens, enrollment criteria for ART, monitoring for CD4 counts, and HIV viral load and adverse effects of ARV. The majority of PLWH on cART in China are able to rapidly achieve virological suppression with fairly good immunological recovery [62–65]. The NFATP has substantially reduced mortality among HIV-infected patients along with increasing coverage of ART. The treatment coverage was 63.4% at the end of 2009 [63]. At the end of 2018, 718,499 (83.4%) out of the total 861,042 PLWH in China were receiving ART [2].

Despite dramatic improvements, China faces serious challenges in maintenance of a sustainable and successful NFATP because of substantial attrition along the continuum of HIV care, including implementation of the test-and-immediately-treat policy and provision of care for individualized health needs of the patients [66, 67, 68••]. The *previous CDC-led AIDS treatment program and mode of management had been transferred to the hospital-based model years ago, which had proved to be effective and successful* [64]. *However, as the body of PLWH continuously increases, the hospital-based model could be suffering from work overload. Pilot programs examining the feasibility and effectiveness of a community-based model for patient management are ongoing, according to China CDC.*

Implications for HIV Control and Prevention in the Next Decade

Our review of the HIV epidemiology in China here focuses primarily on "testing and surveillance," "antiretroviral therapy," and "research" (mostly basic and clinical HIV medicine). First, we address a couple of broad observations, followed by some discussions on challenges and opportunities.

Much has changed since the first case of HIV appeared in China in 1989. The earlier period of the HIV epidemic was localized in IDUs and blood donors. Today, sexual transmission is the dominant mode for infection. Notably, similar to many Western countries, MSM is the highest-risk group. The epidemic has spread to the rest of the country—especially along the coastal regions.

While significant scientific knowledge have been gained from research on many aspects of the basic and clinical HIV medicine (e.g., ART adherence; HIV-1 subtype), we know little regarding how macro-social determinants might contribute to the continued promulgation of the virus. We did not cover macro-social factors on HIV (though they are strongly implied in the *report*). Nonetheless, some of the research reviewed here does provide an opportunity to speculate what (and how) macro-social factors might play a role in China's HIV control and prevention efforts. We briefly address four scenarios pertaining to these macro-social factors.

Despite aggressive and proactive national strategies to promote testing, HIV prevalence and incidence continue to rise, especially among MSM which is the highest-risk group for contracting HIV in China. Notably, due to traditional family values as well as stigma and discrimination toward homosexuals, relatively large numbers of MSM in China are currently married or living with a female partner. It is estimated that approximately 50–70% have had female sexual partners in their lifetime [69]. Such bisexual behaviors and/or relationships are likely to pose HIV risks for the general female population, though at this juncture they are still considered as a low-risk group [70]. Without a deeper understanding of their sexuality and sexual expressions, scaling up HIV testing and surveillance is only a necessary but not a sufficient strategy to halt the epidemic in this population.

In this review, we did not address the utility of pre-exposure of prophylaxis (PrEP), one of the latest tools in the biomedical arsenal in the fight against HIV. Although China's CDC has initiated a pilot program to address this, targeting MSM, unfortunately, lessons learned are less than encouraging. Only a very small number of participants actually enrolled in the use of PrEP (cite), and a fair number dropped out [71]. For example, among those who initially used but subsequently dropped out [72] "… Perception of low HIV risk, mistrust of the national PrEP program, and concerns about side effects were the main reasons for not wanting to use PrEP. Also, lack of main sexual partner's support, difficulties in adhering to the daily TDF regimen, and the inconvenient schedules in securing the medicine were the major reasons for not wanting to use or quitting the use of PrEP." In brief, without a nuanced understanding of the motivations which undergird people's behaviors, it is not likely significant benefits will be gained from just scaling up HIV testing and surveillance.

These types of argument also apply to older men (regardless of sexual identity and/or orientation), in which they now live in a fast-changing society allowing them to engage in sexual expressions (e.g., extramarital affairs, commercial sex) they deem we unlikely merely a few decades ago. Meanwhile, they are likely to have low health and sexual

literacy which place them at-risk for contracting HIV and other non-HIV STIs. Aged- and culturally appropriate health education, coupled with social prevention strategies, need to be a high priority among China's national HIV prevention priorities.

In a study, Hua et al. found HIVDR to be low (2.7%) in eastern China [73]. However, some of the HIVDR in the study were associated with PIs where most of them had not been introduced into the study area at the time. This suggests that HIV drug-resistant isolates from other countries may have "slipped through" into eastern China, which has implications for those individuals relying on the national ART program. There are, at least, two possible, non-mutually exclusive explanations for this "slip through" which might contribute to HIVDR: (1) an underground ARV drug trade and/or (2) Chinese nationals were infected by non-Chinese nationals via sexual mixing.

There is a solid body of global research documenting that negative macro-social factors are contributing to a range of health disparities, including how cultural norms, mores, and/or practices can expose someone to HIV risk [74–79]. China is lagging behind other countries in the study of the effect of macro-social determinants on the HIV-continuum. In brief, it would be a wise investment to integrate some of the macro-social factors into clinical and/or behavioral HIV research.

Funding Information This study was supported by the China National Science and Technology Major Projects on Infectious Diseases (2018ZX10721102-004), the National Natural Science Foundation of China (81773485, 81872671, 81803291), and partially supported by Shanghai Municipal Health and Family Planning Commission (GWTD2015S05).

Compliance with Ethical Standards

Conflicts of Interest The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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